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IN a previous paper in this series evidence was presented that the intravenous injection of minute amounts of adrenalin hastens the clotting of blood.[1] The amounts used did not vary much above or below the amounts discharged by the adrenal glands after brief stimulation of the splanchnic nerves, as determined by Osgood in this laboratory,[2] and may therefore be regarded as physiological. Since injected adrenalin is capable of shortening the coagulation time, might not the increased secretion of the adrenals resulting from splanchnic stimulation likewise have that effect? The answer to that question was the object of the experiments here recorded.

The blood was taken and its coagulation was recorded graphically in the manner previously described.[3] In some instances the cats were etherized, in others they were anaesthetized with urethane, or were decerebrated. The splanchnic nerves always were stimulated after being cut away from connection with the spinal cord. Sometimes the nerves were isolated unilaterally in the abdomen; sometimes, in order to avoid manipulation of abdominal viscera, they were isolated in the thorax and stimulated singly or together. A tetanizing current was used, barely perceptible on the tongue and too weak to cause by spreading any contraction of skeletal muscles.

[1] Cannon and Gray: This journal, 1914, xxxiv, p. 235.
[2] See Cannon, This journal, 1914, xxxiii, p. 369.
[3] See Cannon and Mendenhall: This journal, 1914, xxxiv, p. 225.

The effects of splanchnic stimulation. — That splanchnic stimulation accelerates the clotting of blood, and that the effects vary in different animals, are facts illustrated in the following cases:

Oct. 25. A cat was etherized and maintained in uniform ether anaesthesia. After forty minutes of preliminary observation the left splanchnic nerves were stimulated in the abdomen. Following are the figures which show the effects on the coagulation time:

3.00 — 4 minutes	4.03 — 2.5 minutes
.07 — 5.5 "	.07 — 2.5 "
.14 — 4 "	.11 — 3 "
.32 — 4.5 "	.16 — 2 "
.39 to .40 Stim. left spl.	.20 — 1.5 "
.42 — 5 minutes	.23 — 4 "
.49 — 5 "	.29 — 5.5 "
.56 — 2 "	.40 — 5.5 "
4.00 — 1 "	.50 — 5 "

In this instance at least ten minutes elapsed between the end of stimulation and the beginning of faster clotting. The period of faster clotting, however, lasted for about a half-hour, during which the coagulation time averaged 2.1 minutes, only 43 per cent of the previous average of 4.8 minutes. It is noteworthy that the curve (see Figure 1), while lower, shows oscillations not unlike those which follow injection of adrenalin.[1]

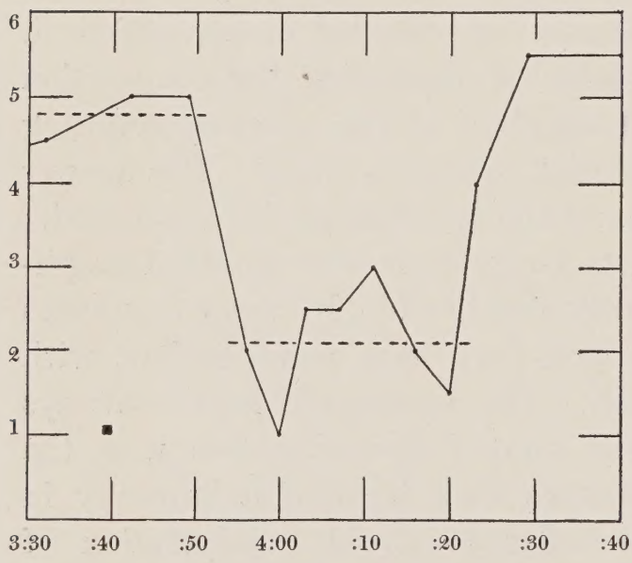

FIGURE 1. Shortening of coagulation time after stimulation of the left splanchnic nerves 3.39 — .40.

The primary delay of the effect is not always, indeed it is not commonly, present:

Nov. 6. A cat was anaesthetized (1.40 P.M.) with urethane, and later (3.05) its brain was pithed. The following observations on the

[1] Cf. CANNON and GRAY: This journal, 1914, xxxiv, p. 239.

coagulation time show the prompt effect of splanchnic stimulation:

3.36 — 7 minutes
.46 — 6 "
4.02 to .05 Stim. left spl. in abdomen
.08 — 4 minutes
.10 — 3 "
.18 — 3.5 "
.23 — 6.5 "

In Figure 2 is presented the original record of the shortening of coagulation after stimulation of the left splanchnic nerve (Nov. 8), in a cat with brain pithed.

In the foregoing instances the coagulation time was reduced after splanchnic stimulation to less than half what it was before. The reduction was not always so pronounced.[1]

Nov. 7. A cat maintained in uniform ether anaesthesia with artificial respiration had the following changes in the clotting time of its blood as the result of stimulating the left splanchnic nerve in the thorax:

3.40 — 5 minutes	4.11 — 4 minutes
.45 — 5 "	.16 — 3.5 "
.51 — 5.5 "	.21 — 4 "
.58 to 4.00 Stim. left spl.	.26 — 4.5 "
4.01 — 4.5 "	.31 — 5 "
.06 — 3.5 "	.36 — 6.5 "

In this case the average for about 15 minutes before stimulation was slightly over 5 minutes, and for 25 minutes thereafter it was four minutes.

[1] This animal had just passed through a period of excitement with rapid clotting (see CANNON and MENDENHALL: This journal, 1914, xxxiv, p.258.).

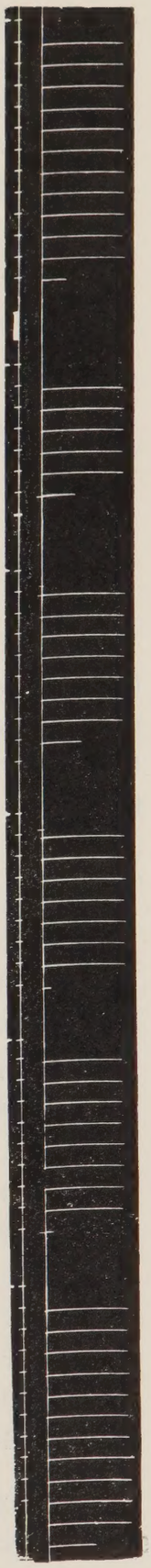

FIGURE 2. About two-fifths original size. Record of shortening of coagulation time after stimulation of the left splanchnic nerves, 4.33 — .35. The time before stimulation was 6 minutes, and afterwards 3, 4, 4, 4.5, and 6 minutes.

In all cases thus far the period of shortened coagulation lasted from 10 to 30 minutes. In other cases, however, the effect was seen only in a single observation. If this had occurred only once after splanchnic stimulation, it might be attributed to accident, but it was not an infrequent result, e.g.:

Oct. 28. A cat was etherized and decerebrated and the splanchnic nerves were isolated in the thorax. Following are two instances of brief shortening of coagulation after splanchnic stimulation:

3.36 — 4.5 minutes	4.07 — 4.5 minutes
.42 — 4.5 "	.12 — 5.5 "
.47 to .49 Spl. stim.	.19 to .22 Spl. stim.
.51 — 4.5 minutes	.23 — 3.5 minutes
.57 — 2 "	.27 — 4 "
4.01 — 4 "	.33 — 5 "

In the foregoing instance it is noteworthy that the degree of acceleration is not so great after the second stimulation of the splanchnics as it was after the first. This reduction of effect as the nerves were repeatedly stimulated was frequently noted. The following case presents another illustration:

Nov. 12. A cat was etherized (2.35 P.M.) and piqûre was performed (3.12) upon it. The operation was without effect. The loss or lessening of effectiveness on second stimulation of the left splanchnic nerves is to be compared with the persistence of effectiveness on the right side:

3.40 — 4.5 minutes	3.39 — 4 minutes
.45 — 4.5 "	.44 — 4 "
.54 to .56 Stim. left spl. in abd.	.48 — 4 "
4.00 — 3 minutes	.55 to .57 Stim. right spl.
.05 — 2 "	.59 — 3 minutes
.10 — 5.5 "	5.02 — 2.5 "
.16 — 5 "	.07 — 3 "
.22 to .27 Stim. left spl. in abd.	.11 — 3 "
.30 — 4 minutes	.15 — 5.5 "
.34 — 4 "	.22 — 5.5 "

The experiments above recorded show that stimulation of the splanchnic nerves results immediately, or after a brief period, in a

shortening of the coagulation time of the blood — an effect which in different animals varies in duration and intensity, and diminishes as the stimulation is repeated. The next question is whether this effect is produced through the adrenal glands.

The effect of splanchnic stimulation with and without the adrenal glands. — The manner in which splanchnic stimulation produces its effects is indicated in the following experiments:

Nov. 28. A cat was etherized and pithed through the orbit to the mid-thorax. The blood vessels of the *left* adrenal gland were then quickly tied and the gland removed. The readings for a half hour before the left splanchnic nerve was stimulated averaged 7 minutes, then, —

4.38 to 40 Stim. left spl. (glandless)
.42 — 7 minutes
.50 — 7 "
5.02 to .04 Stim. right spl.
.06 — 4 minutes
.10 — 7 "
.18 — 7 "
.26 — 7 "

Dec. 4. A cat was etherized and pithed through the orbit to the neck region. The right and left splanchnic nerves were tied and cut in the thorax. The *left* adrenal gland was then carefully removed. These operations consumed about a half-hour. The following records show the effect of stimulating the left and right splanchnic nerves:

4.10 — 5 minutes
.16 — 4.5 "
.25 to .28 Stim. left spl. (glandless)
.30 — 4.5 minutes
.35 — 4.5 "
.40 — 7.5 "
.49 to .51 Stim. right spl.
.55 — 4.5 minutes
5.00 — 2.5 "
5.14 — 6 minutes
.23 to .25 Stim. right spl.
.26 — 6 minutes
.33 — 4.5 "
.38 — 3.5 "
.43 — 4.5 "
.49 — 5 "
.55 — 6 "

The results in this experiment are represented graphically in Figure 3.

Elliott has presented evidence that in the cat the splanchnic innervation of the adrenals is not crossed, so that if the gland is removed on one side stimulation of the nerves on that side causes no discharge from the opposite gland.[1] As the above experiments clearly show, splanchnic stimulation on the glandless side results in no shortening of the coagulation time; whereas, in the same

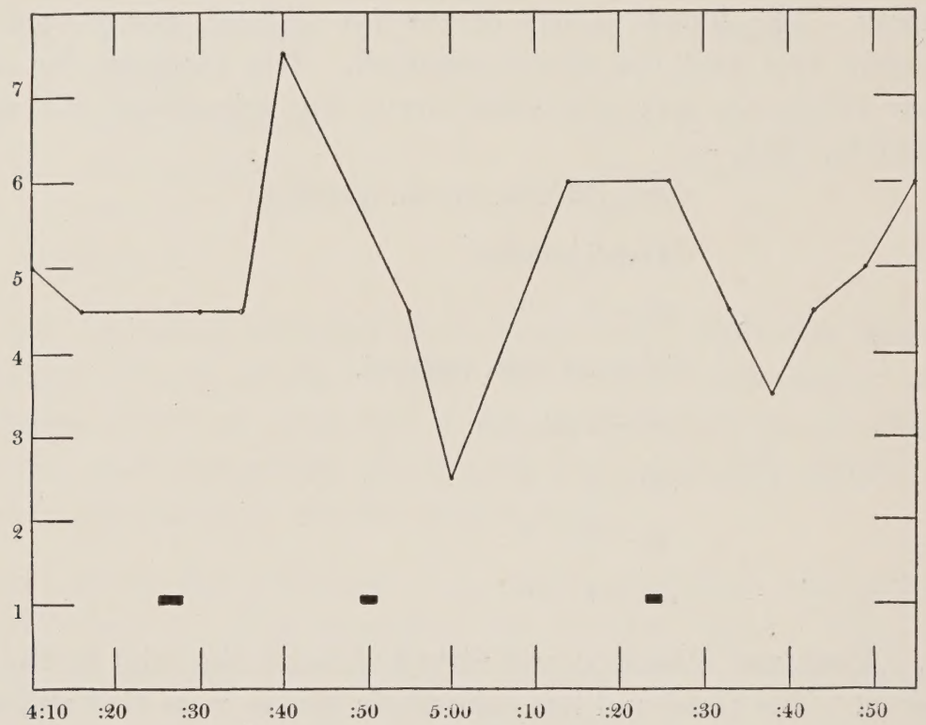

FIGURE 3. Results of stimulating the left splanchnic nerves, 4.25 — 28, after removal of the left adrenal gland, and of stimulating the right splanchnic nerves, 4.49 — .51 and 5.23 — .25, with right adrenal gland present.

animals, stimulation of the nerves on the other side (still connected with the adrenal gland) produces a sharp hastening of the clotting process.

The splanchnics innervate the intestines and liver even though the adrenal gland is removed. The foregoing experiments indicate that the nerve impulses delivered to these organs do not influence them in any direct manner to accelerate the speed of coagulation. Indeed in one of the experiments (Dec. 4, p. 247) a high reading about ten minutes after splanchnic stimulation on the glandless side suggests the possibility of an opposite effect. Direct stimulation

[1] ELLIOTT: Journal of physiology, 1912, xliv, p. 405.

of the hepatic nerves on one occasion was followed by a change of the clotting time from 4.5, 5, 4.5, 4.5 minutes during 25 minutes before stimulation to 4.5, 7, and 6 minutes during 20 minutes after stimulation.

Since with the adrenals present stimulation of hepatic nerves induces glycogenolysis and quick increase of blood sugar,[1] just as splanchnic stimulation does, the failure of the blood to clot faster after stimulation of the hepatic nerves confirms the evidence already offered that faster clotting in hyperadrenalinaemia is not due to hyperglycaemia.[2]

The liver and intestines cannot be made to shorten clotting time by stimulation of their nerves, but, as has already been shown, neither can adrenalin act by itself to hasten the clotting process.[3] Apparently the effect is produced by coöperation between the adrenals and the liver (and possibly also the intestines). Somewhat similar cooperation is noted in the organization of sugar metabolism; splanchnic stimulation in the absence of the adrenal glands does not increase blood sugar,[4] and in the absence of the liver adrenalin is without influence.[5]

The variations of effect noted after splanchnic stimulation can be accounted for by variations in the adrenalin content of the glands. Elliott reports that animals newly brought into strange surroundings may have a considerably reduced amount of adrenalin in their adrenals.[6] The animals used in our experiments had been for varying lengths of time in an animal house in which barking dogs were also kept, and were therefore subject to influences which would be likely to discharge the glands.

[1] MACLEOD: Diabetes: its Pathological Physiology, London, 1913, pp. 68–72.

[2] See CANNON and GRAY: This journal, 1914, xxxiv, p. 241.

[3] See CANNON and GRAY: *loc. cit.*, p. 240.

[4] GAUTRELET and THOMAS: Comptes rendus de la Société de Biologie, 1909, lxvii, p. 233.

[5] BANG: Der Blutzucker, Wiesbaden, 1913, p. 87.

[6] ELLIOTT: *loc. cit.*, p. 379.

Summary

Stimulation of the splanchnic nerves results immediately, or after a brief delay, in shortening of the coagulation time of blood. The degree and the duration of the effect varies, — clotting not uncommonly takes less than half the time it took before stimulation, and this period of rapid clotting may last from 10 to 30 minutes.

The stimulation usually produces less marked effects as it is repeated.

If the adrenal gland is removed on one side, splanchnic stimulation on that side does not shorten the clotting time; whereas splanchnic stimulation on the other side is still effective. The faster clotting is therefore due to increased adrenal discharge.

Since stimulation of nerves supplying the liver and intestines does not hasten clotting, and since increase of adrenalin has no effect in the absence of the liver and intestines, the shortened clotting after splanchnic stimulation is accounted for by the action of adrenal discharge on the liver (and intestines?).

The variations in the effects in different animals can be accounted for by variations in the adrenalin content of the adrenal glands in confined animals.

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